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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,039	07/12/2001	Shoulian Dong	3218.2A	3123

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AFFYMETRIX, INC
ATTN: CHIEF IP COUNSEL, LEGAL DEPT.
3380 CENTRAL EXPRESSWAY
SANTA CLARA, CA 95051

EXAMINER	
KIM, YOUNG J	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,039	DONG ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-53,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-53,57 and 58* is/are rejected.

7)☒ Claim(s) *39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on April 23, 2004 has been entered.

Preliminary Remark

The Office acknowledges the cancellation of claims 1-38, 54-56, and 59-173.

Claims 39-53, 57, and 58 are pending and are under prosecution therefore.

Information Disclosure Statement

The IDS received on April 23, 2004 is acknowledged. A signed copy of its corresponding PTO-1449 is attached hereto.

Drawings

The drawings filed on February 26, 2002 are acceptable.

Claim Objections

Claim 39 is objected to because of the following informalities: claim 39 recites the phrase, "providing a nucleic acid array comprising probes to ***a*** interrogate the genotype of a plurality of..." which appears to contain a typographical error (the article, "a"). It appears that the article should be deleted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 and its dependent claim 58 are indefinite for the recitation of the step, "hybridizing said second nucleic acid sample to said array," because the steps previous to the instant step produces ***DNA duplexes*** (not second nucleic acid sample), followed by the isolation of the DNA duplexes, rendering the instant step indefinite in what is considered to be the second nucleic acid sample. Since the step of, "producing a second nucleic acid sample" generates many intermediate products, absent a clear recitation that the DNA duplexes ***are*** the second nucleic acid sample, a reference to "second nucleic acid sample" could be confusing as it could refer to any of the intermediate products produced under the step of, "obtaining a second nucleic acid sample."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 47 is dependent on claim 39.

Claim 39 requires the steps of: a) providing a 1st nucleic acid sample; b) fragmenting the 1st nucleic acid sample; c) ligating adaptor sequences to the fragments; d) amplifying the fragments to which adaptors are ligated; e) providing a nucleic acid array; f) hybridizing the sample to said nucleic acid array; and g) analyzing the hybridization pattern.

Claim 47 depends from claim 39, wherein said claim requires that the, "***entire method***" is performed in ***a single reaction vessel***.

Therefore, the claim requires that a single reaction vessel execute the steps (a) through (g).

It would require an undue experimentation to practice the claimed method because some of the steps required in claim 47 cannot be achieved in a single reaction vessel. For example, the method not only requires that a fragmentation, ligation, and amplification be done in a single reaction vessel, but the presence of microarray and its hybridization and its analysis all be conducted in a single reaction vessel. Neither the prior art nor the specification would allow a skilled artisan to design a single reaction vessel which would contains all of the required elements for the "entire method" to be conducted.

For the above reasons, it would require the skilled artisan an undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCaskey et al. (U.S. Patent No. 6,100,030, issued August 8, 2000, priority January 10, 1997) in view of DeRisi et al. (Science, October 1997, vol. 278, pages 680-686) and Moyer et al. (Applied and Environmental Microbiology, July 1996, vol. 62, no. 7, pages 2501-2507).

Claim 39 is drawn to a method of analyzing a first nucleic acid sample by fragmenting the first nucleic acid, ligating adaptor sequences to the resulting fragments, amplifying the ligated fragments and hybridizing the resulting amplified ligated fragments to a nucleic acid array and analyzing their hybridization pattern. Newly added limitation to this claim requires a computer to predict the fragmented nucleic acids, and provides a microarray comprising probes for these fragmented nucleic acids for the subsequent hybridization assay.

Some embodiments are drawn to the percentage of second nucleic acid sample produced by the fragmentation method (claims 40-43).

Some embodiments are drawn to the first nucleic acid being a DNA (claim 44), genomic DNA (claim 45), cDNA (claim 46).

Some embodiments are drawn to the nature of the fragmentation produced by a restriction enzyme (claim 48), a type IIs endonuclease (claim 49).

Some embodiments are drawn to the nature of the adaptor sequence (claim 50 and 51).

The method is also drawn to detecting a sequence variation in the nucleic acid (claim 52), wherein the variation is a single nucleotide polymorphism (SNP) (claim 53).

McCaskey Feazel et al., hereto referred to as '030 patent, disclose a method for detecting polymorphism (column 23, line 40; column 22, lines 33-37; **claim limitation 52 and 53**) in a nucleic acid sample by fragmenting genomic DNA (column 18, lines 20-21; **claim limitation 44 and 45**), ligating adaptor sequences to the resulting fragments (column 18, lines 24-25), wherein the adaptor sequences are complementary to the PCR primer sequences (column 18, lines 25-29 and 60-63; **claim limitation 50-51**), amplifying the adaptor ligated fragments and hybridizing them to a microarray comprising an array of nucleic acids which are complementary to the amplified, adaptor ligated fragments (column 23, lines 54-60). The method of the '030 patent employs a restriction endonuclease (column 18, line 21; **claim limitation 48 and 49**) for producing the nucleic acid fragments. The '030 patent discloses that any type of restriction endonuclease known in the art can be used to digest the DNA for its analysis (column 18, line 36-38).

The '030 patent does not teach the amplified adaptor ligated nucleic acids (or second nucleic acids) comprising various percentage of the initial DNA population (claims 40-43), nor the DNA as being a cDNA produced from an RNA molecule (claim 46). The '030 patent also does not *explicitly* teach a method of determining the sequence of the probes of the microarray by a computer system, wherein the computer system is employed to predict the fragmented nucleic acid sequences.

Moyer et al. disclose a method of employing a computer simulation to predict fragmented nucleic acid sequences (page 2501, 2nd column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of the '030 patent with the conventional knowledge in the art to arrive at the invention as claimed for the following reasons.

Although the '030 patent does not explicitly teach that the amplified, adaptor ligated nucleic acid (or second nucleic acids) comprises various percentage of the first nucleic acid population, the patent clearly demonstrates producing fragments which, by inherency, would have a varying degree of percentage of the first nucleic acid population.

Although the '030 patent does not use cDNAs produced from RNAs (claim limitation 46) for fragmentation, such knowledge, as demonstrated by DeRisi et al., is also within the purview of an ordinarily skilled artisan in the field of array hybridization:

"[v]irtually all differences in cell type of state are correlated with changes in the mRNA levels of many genes. This is fortuitous because the only specific reagent required to measure the abundance of the mRNA for a specific gene is a cDNA sequence." (DeRisi at page 680, 1st column)

The cDNA is disclosed as being derived from mRNA by reverse transcription process and hybridized to a DNA array (DeRisi at page 680, 3rd column).

Therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in substituting the genomic DNA of '030 patent with the cDNA of DeRisi et al. because both types of DNAs were demonstrated to be hybridizable to DNA arrays. Furthermore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in arriving at the claimed method which

involves a computer to predict the fragmented sequence given the computer-simulation method disclosed by Moyer et al. with the motivation provided by the '030 patent, wherein it states:

"In one preferred embodiment, AFLP is used to identify differentially amplified nucleic acids, which are then converted into polynucleotide probes which map to polymorphisms. The differentially amplified AFLP DNAs are ***converted into polynucleotide probes*** by isolating individual polymorphic AFLP fragments from a mixture fragments in an AFLP amplification product, followed by using these isolated fragments (or clones or subclones thereof) as polynucleotide probes in ***hybridization with immobilized DNA amplification mixtures (e.g., AFLP products)***." (column 3, lines 27-36).

As the '030 patent motivates an ordinarily skilled artisan to employ the AFLP generated DNAs for array probes, the artisan would have had a reasonable expectation of success in taking this motivation with the computer simulation which predicts restriction fragments for the advantage of efficaciously, "detecting and differentiating...genes" (Moyer et al., page 2501, 2nd column and Abstract).

Therefore, the invention as claimed is obvious over the cited references.

Applicants' arguments received with the RCE request, received on April 23, 2004 have been fully considered but they are not found persuasive for the following reasons.

Claim 39 has been amended to include the limitation, of providing a nucleic acid array comprising probes to interrogate the genotype of a plurality of polymorphisms present on the fragmented sample. Such limitation, however, is considered obvious in view of the teachings provided by the '030 patent wherein the patent states that, "AFLP is used to identify differentially amplified nucleic acid, which are then ***converted into polynucleotide probes which***

map polymorphism." (column 3, lines 27-36). As the '030 patent employs such techniques to design probes for mapping polymorphisms, one of ordinary skill in the art at the time the invention was made would have been motivated to employ the derived polynucleotide probes into an array of nucleic acid for the obvious advantage of simultaneous detection of a plurality of markers. As to the limitation of, "wherein a computer system is used to predict polymorphisms present on fragments in the second nucleic acid sample," it is not clear that this procedure is in any way related to the nucleic acid array or the method of analyzing a first nucleic acid sample since the above limitation has no correlation to the nucleic acid array. The recited limitation also do not have any correlation to the claimed method of analyzing a first nucleic acid sample since the method analyzes the hybridization pattern resulting from the hybridization and not from the computer system.

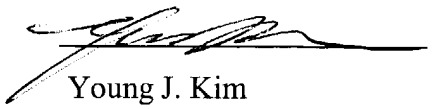
Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should

be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (517) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0507.



Young J. Kim
Patent Examiner
Art Unit 1637
6/13/04

yjk